

REMARKS

This *Response* and *RCE* are filed in reply to the final *Office Action* mailed on May 28, 2010 and the *Advisory Action* mailed on September 22, 2010. Claims 10, 16-18, 50, 51, 53-55, 64, 65, 67-69, 71, 72, 74, 76, 77, 79-82, 84-87, 89-92, 95-98, 100, 102-106, and 108-11 are currently pending and stand rejected under 35 U.S.C. §103(a). The Specification was objected to on several grounds in the *Office Action* and in the *Advisory Action*. The Drawings were found to not be noncompliance with CFR 1.121(d) in the *Office Action*, but replacement sheets filed in the *Amendment* on September 10, 2010 were found to be acceptable according to the *Advisory Action*.

Applicants submit this *Response* and *RCE* solely to facilitate prosecution. As such, Applicants reserve the right to pursue claims of broader or similar scope as originally filed in a continuation application or other application after allowance of the present Application. Applicants do not concede that any current or past rejections are correct and reserve the right to challenge such rejections later in prosecution or on appeal. Accordingly, any amendment, argument, or claim cancellation is not to be construed as abandonment or disclaimer of subject matter. As certain of the current amendments may include broadening amendments, Applicants respectfully request the Examiner to revisit any previously reviewed references cited in this Application to further ensure that the currently pending claims remain patentable over any previously reviewed references.

I. Specification

A. List of References

The Specification was objected to in the *Office Action* as containing documents that were improperly incorporated by reference because “the complete bibliographical citation has not been provided” and “a review of the original specification fails to find where any bibliographical index has been provided.” *Office Action*, May 28, 2010, page 2-3, ¶¶3-4. Applicants had previously amended the specification to include detailed bibliographic information for the cited publications in the Substitute Specification filed with the *Amendment* of September 10, 2010. According to the *Advisory Action*, this amendment has not been entered, and the Examiner asserts that this information was not adequately supported by the original disclosure and therefore represents new material. Applicants respectfully traverse this rejection for the following reasons.

First, Applicants note that the listing of references can be found in the original provisional application 60/216,594 at Attachment A. Amendments to the Specification incorporating the full bibliographic description were drawn from the list filed in the original provisional, which was incorporated by reference. For this reason alone, the full bibliographic references provided in the substitute specification do not constitute new matter.

Second, Applicants also note that this rejection has been raised in other Applications in this patent family and has been resolved. In particular, Applicants note that USSN 11/648,713 made a similar amendment to incorporate these references, and that amendment was initially rejected by the Examiner. However, the rejection was challenged in a Pre-Appeal Brief Request. *See* USSN 11/648,713, Pre-Appeal Brief Request for Review mailed January 24, 2011, page 4. The Panel in that instance returned the application for examination and the rejection was dropped in the following Office Action. As such, the rejection in the '713 application was moot, and should now be moot in this application as well.

B. Amino Acid Sequences

In the Advisory Action, the Examiner raises a new issue regarding the amendments to the specification of the present application. Specifically, “a review of the original disclosure fails to provide support for the now explicit recitation of amino acid sequence (SEQ. ID. NO. 11)...., or the recitation of specific amino acid at pages 77-82 of the marked-up copy of the specification...” *Advisory Action* mailed September 22, 2010, page 2. Applicants respectfully disagree with this assertion and traverse.

First, the Specification as originally filed specifically stated “the **native** *Taq* polymerase.” *See* 09/901,783, *Specification* filed on July 9, 2001, page 64 (emphasis added.) The structural sequence of native *Taq* polymerase is known in the art and has been described in at least three references: Eom, S.H., et al, “Structure of *Taq* polymerase with DNA at the polymerase active site.” *Nature* **382**, 278-281, (1996); Li, Y., et al. “Crystal structure of open and closed forms of binary and ternary complexes of the large fragment of *Thermus aquaticus* DNA polymerase I: structural basis for nucleotide incorporation.” *EMBO J.*, **17**(24): 7514-7525 (1998); Li, Y. et al., “Crystal Structure of the Klenow fragment of *Thermus aquaticus* DNA polymerase I complexed with deoxyribonucleoside triphosphates.” *Protein Science* **7**, 1116-1123 (1998.) As noted above, these references were filed in the original provisional to which the present application claims priority, and were incorporated by reference. The references can also be found page 39 of

the original specification as filed on July 9, 2001. The amino acid sequence Seq. ID No. 11 was specifically disclosed in the Sequence Listing filed on March 11, 2004. Seq. ID No. 11 is listed as the protein *Thermus aquatius*, i.e. *Taq* polymerase. Because the original specification stated “the native *Taq*,” references describing the known amino acid sequence of native *Taq* were incorporated by reference from the provisional and cited in the nonprovisional, and the accepted Sequence Listing in the application specifically discloses that *Taq* sequence, the explicit addition of the known and disclosed amino acid sequence to the instant Specification does not constitute new matter, and does have adequate support in the original application.

Second, the amino acid sequences found on pages 77-82 are also specifically disclosed in the original application at pages 65-67. *See* 09/901,783, *Specification* filed on July 9, 2001. The original specification disclosed those sequences and therefore the current amendment cannot constitute new matter, and does have adequate support in the original application.

Finally, these amendments are consistent with other amendments that were made and accepted by the Patent Office in related applications. For example, U.S. Patent 7,329,492 discloses these sequences in Columns 51-54. Current U.S. Patent Application Publication 2007-0172868 discloses these sequences on pages 29-30. No rejection based on inadequate support was made in those cases.

For the reasons discussed above, the rejections of amendments to the specification for the references and for the amino acid sequences are improper. The amendments currently made in the instant specification have support in the specifications of the provisional and non-provisional application and therefore do not new matter. Applicants respectfully request that the rejections be withdrawn and that the amendments to specification be entered.

II. Rejection under §103(a)

Claims 10, 16-18, 50, 51, 53-55, 64, 65, 67-69, 71, 72, 74, 76, 77, 7982, 84-87, 89-92, 95-98, 100, 102-106, and 108-111 were rejected under 35 U.S.C. § 103(a) as purportedly obvious over U.S. Patent No. 6,982,146 to Schneider et al. (“Schneider”) in view of U.S. Patent No. 7,037,687 to Williams *et al.* (“Williams et al.”) and U.S. Patent No. 6,306,607 to Williams (“Williams”). *See Final Office Action* mailed May 28, 2010, Pages 5-11, ¶¶ 9-32. These rejections are respectfully traversed at least because Schneider and Williams cannot be combined as the Examiner suggests because their teachings are incompatible and the proposed combination

would result in an inoperable method. Under established precedent, such a combination cannot support an obviousness rejection.

"A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103(a). Underlying factual determinations in an obviousness analysis include (1) the scope and content of the prior art, (2) the level of ordinary skill in the art, (3) the differences between the claimed invention and the prior art, and (4) objective indicia of nonobviousness. *Merck & Co. v. Teva Pharms. USA, Inc.*, 395 F.3d 1364, 1369 (Fed. Cir. 2005) (citing *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966)).

Applicants respectfully submit that a *prima facie* case of obviousness against Claims 10, 16-18, 50, 51, 53-55, 64, 65, 67-69, 71, 72, 74, 76, 77, 79-82, 84-87, 89-92, 95-98, 100, 102-106, and 108-111 due to Schneider in view of Williams et al. or Williams has not been made.

It is important to recognize that each of Claims 10, 16-18, 50, 51, 53-55, 64, 65, 67-69, 71, 72, 74, 76, 77, 79-82, 84-87, 89-92, 95-98, 100, 102-106, and 108-111 must be considered as a whole. See, e.g., *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1742 (2007) ("What matters is the objective reach of the claim."); *Datascope Corp. v. SMEC, Inc.*, 776 F.2d 320, 324 (Fed. Cir. 1985) (noting that the references must be considered "as a whole" and that the claimed subject matter must be considered "as a whole."). Considering each of Claims 10, 16-18, 50, 51, 53-55, 64, 65, 67-69, 71, 72, 74, 76, 77, 79-82, 84-87, 89-92, 95-98, 100, 102-106, and 108-111 as a whole is important because "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR*, 127 S. Ct. at 1741. That is because "inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known." *Id.*

Applicants respectfully submit that only by using impermissible hindsight would one modify Schneider, Williams *et al.*, and Williams as the Examiner suggests to arrive at

Applicants' Claims 10, 16-18, 50, 51, 53-55, 64, 65, 67-69, 71, 72, 74, 76, 77, 79-82, 84-87, 89-92, 95-98, 100, 102-106, and 108-111. Yet, factfinders must avoid the distortion caused by hindsight bias "and must be cautious of arguments reliant upon ex post reasoning." *KSR*, 127 S. Ct. at 1742 (citing *Graham* and "warning against a 'temptation to read into the prior art the teachings of the invention in issue' and instructing courts to 'guard against slipping into the use of hindsight.'").

The principle of operation of Schneider is a FRET interaction between a donor on a polymerase and an acceptor on a nucleotide. However, the Examiner admits that Schneider does not teach that the fluorescent label is released from the nucleotide by action of the polymerase (see *Final Office Action mailed May 28, 2010, Page 8, ¶ 23*) and that neither Schneider nor Williams et al. have been found to disclose using a nucleotide where the fluorescent label is attached to a terminal phosphate. See *Final Office Action mailed May 28, 2010, Page 9, ¶ 28*.

Williams is alleged to teach a nucleotide comprising a label attached to a terminal phosphate. However, that is not a complete description of the teachings of Williams. Williams only teaches nucleotides comprising a fluorophore attached to the y-phosphate that also comprise a quencher moiety. See *Williams at Abstract; at Column 3, Lines 36-58*. The principle of operation of Williams is detection of the fluorescent label after it is released from the quencher.

Thus, the principle of operation of the method of Schneider is incompatible with the principal of operation of the method by Williams. **Combination of each with the other would defeat the principle of both.** The presence of the quencher moiety of Williams nucleotides would defeat the principle of FRET transfer between the donor and acceptor in the method described by Schneider. Modification of the Williams nucleotides to remove the quencher moiety would render the nucleotides unsuitable for their intended purpose. Because of this, one of ordinary skill in the art, prior to Applicants' invention, would not have modified Schneider and Williams as the Examiner suggests.

If a proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. The Federal Circuit's comments in *McGinley v. Franklin Sports, Inc.*, are

instructive:

We have noted elsewhere, as a "useful general rule," that references that teach away cannot serve to create a prima facie case of obviousness. In re Gurley, 27 F.3d 551, 553, 31 USPQ2d 1130 (Fed. Cir. 1994). **If references taken in combination would produce a "seemingly inoperative device," we have held that such references teach away from the combination and thus cannot serve as predicates for a prima facie case of obviousness.** In re Sponnoble, 405 F.2d 578, 587, 160 USPQ 237, 1244, 56 C.C.P.A. 823 (1969) (references teach away from combination if combination produces seemingly inoperative device); *see also In re Gordon*, 733 F.2d 900, 902, 221 USPQ 1125, 1127 (Fed. Cir. 1984) (inoperable modification teaches away).

McGinley v. Franklin Sports, Inc., 262 F.3d 1339, 1353-54 (Fed. Cir. 2001) (emphases added); *see also Tec Air, Inc. v. Denso Mfg. Michigan Inc.*, 192 F.3d 1353, 1360 (Fed. Cir. 1999) (noting that there "is no suggestion to combine, however, if a reference teaches away from its combination with another source" and that "[i]f when combined, the references 'would produce a seemingly inoperative device,' then they teach away from their combination."). Removal of the quencher moiety from the Williams nucleotides would be contrary to the principle of operation taught in Williams and would render the nucleotides unsatisfactory for their intended purpose.

Thus, either way one considers the proposed combination of Schneider and Williams, there could not have been any motivation to modify the publications as would be required to make the proposed combination. Williams et al. has not been alleged and does not cure the deficiencies of Schneider and Williams.

Because a *prima facie* case of obviousness against Claims 10, 16-18, 50, 51, 53, 55, 64, 65, 67-69, 71, 72, 74, 76, 77, 79-82, 84-87, 89-92, 95-98, 100, 102-106, and 108-111 based upon Schneider, Williams et al., and Williams has not been made, Applicants respectfully request withdrawal of the 35 U.S.C. § 103(a) rejection thereof.

CONCLUSION

By the present *Amendment* and *Request for Continued Examination*, Applicants assert that this *Application* has been placed in full condition for allowance. Accordingly, Applicants respectfully request early and favorable action. The fee for a five month extension of time of \$2350 and fee for a *Request for Continued Examination* of \$810 are included. An IDS is also filed herewith under §1.97(b)(4) for which no fee is due. No additional fees are believed due; however, the Commissioner is hereby authorized to charge any fees that may be required, or credit any overpayment, to Deposit Account No. 20-1507. Should the Examiner have any further questions or reservation, the Examiner is invited to telephone the undersigned at (404) 885-2708.

Respectfully submitted,

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